COVID-19 感染对脑卒中病死率影响的 Meta 分析

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【摘要】背景 新型冠状病毒病 (COVID-19)在全球范围内蔓延，严重影响人类健康和生活。有研究报道 COVID-19 感染可导致血栓性疾病，而脑卒中与血栓事件密切相关。**目的** 评估 COVID-19 感染对脑卒中病死率的影响，并对其可能机制进行探讨，从而为 COVID-19 患者的科学防治提供可靠的临床理论依据。**方法** 通过检索 Web of Science，Pubmed，embase，cochrane，知网及万方等自 2019 年 12 月至 2022 年 1 月发表的文献，筛选 COVID-19 合并脑卒中的相关文献，采用 NOS 风险评价标准对纳入文献进行质量评价，采用 Meta 分析评价 COVID-19 感染对脑卒中病死率的影响，采用漏斗图评价文献发表偏倚。**结果** 共纳入 20 篇文献。Meta 分析结果显示：脑卒中患者中感染 COVID-19 患者的病死率高于非 COVID-19 感染组(RR=4.16, 95% CI: 2.82-6.13, P<0.001)；COVID-19 感染对凝血酶原时间（PT）影响变化更大 (MD=0.93, 95% CI: 0.26-1.60, P=0.007)；COVID-19 感染合并脑卒中 D-二聚体更高(MD=1.34, 95% CI: 0.83-1.84, P<0.001)。两组活化部分凝血酶原时间（activated partial thromboplastin time, APTT）比较，差异均无统计学意义(MD=2.51, 95% CI: -2.69-7.71, P=0.34)；感染 COVID-19 的脑卒中患者年龄更小（MD=-1.70, 95% CI: -3.11--0.28,*P*=0.02）；感染 COVID-19 的脑卒中患者预后与入院时 NIHSS 较高相关（MD=6.66, 95% CI: 4.54-8.59, *P*<0.01），**结论** COVID-19 感染可增加脑卒中的病死率，PT、D-二聚体等凝血系统的改变可能在其中发挥着重要的作用机制，其预后与年龄、入院时的 NIHSS 等危险因素相关。

【关键词】COVID-19；脑卒中；新型冠状病毒；脑血管病；死亡率；

Meta-analysis of the impact of COVID-19 infection on stroke mortality

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【Abstract】Background Novel Coronavirus disease (COVID-19) is spreading globally, seriously affecting human health and livelihood. It has been reported that COVID-19 infection can lead to thrombotic disease, and stroke is closely related to thrombotic events. **Objective** To evaluate the impact of COVID-19 infection on the mortality of stroke, and to explore its possible mechanism, so as to provide a reliable clinical theoretical basis for scientific prevention and treatment of COVID-19 patients. **Methods** We searched the literatures published from December 2019 to January 2022 on Web of Science, Pubmed, Embase, Cochrane, CNKI and Wanfang to screen the literatures related to COVID-19 and stroke. NOS risk assessment criteria were used to evaluate the quality of the included literature, meta-analysis was used to evaluate the impact of COVID-19 infection on stroke mortality, and Begger test and funnel plot were used to evaluate literature publication bias. **Results** A total of 20 literatures were included. Meta-analysis results showed that the mortality of stroke patients infected with COVID-19 was higher than that of non-COVID-19 patients (RR=4.16, 95%CI: 2.82-6.13, P<0.001). The influence of COVID-19 infection on prothrombin time (PT) was greater (MD=0.93, 95%CI: 0.26-1.60, P=0.007); D-dimer

was higher in PATIENTS with COVID-19 infection and stroke (MD=1.34, 95%CI: 0.83-1.84, P<0.001). There was no significant difference in the activated partial thromboplastin time (APTT) between the two groups (MD=2.51, 95% CI: -2.69-7.71, P=0.34); Stroke patients infected with COVID-19 were younger (MD=-1.70, 95%CI: -3.11--0.28,P=0.02); Prognosis of stroke patients infected with COVID-19 was associated with higher NIHSS at admission (MD=6.66, 95% CI: 4.54-8.59, P<0.01). **Conclusion** COVID-19 infection can increase the mortality of stroke, PT, D-dimer and other coagulation system changes may play an important role in this mechanism. The prognosis was related to risk factors such as age and NIHSS at admission.

【**Key words**】COVID-19; Stroke; novel coronavirus; Cerebrovascular disease; Mortality;

2019 年 12 月开始新型冠状病毒病 (coronavirus disease 2019, COVID-19)在全球范围内蔓延，严重影响人类健康和生活。2020 年 3 月上旬，世界卫生组织(World Health Organization , WHO)宣布 2019 年爆发的 COVID-19 感染性疾病为国际关注的突发公共卫生事件[1]。自此该病引起了全球研究者的广泛关注。脑卒中是全球重大公共卫生问题，在世界范围内脑卒中是第二死亡疾病和第三致残疾病，给社会和个人造成了极大负担。在我国脑卒中已超过心血管疾病成为发病率、病死率和致残率最高的疾病。COVID-19 感染不仅仅是肺部受累，还可能累及多器官、多系统[2]，部分文献报道了 COVID-19 影响神经系统，特别是可以引起脑血管疾病[3,4]。大多数关于 COVID-19 与脑卒中相关的报道都集中在如何护理此类患者[5]、护理系统发生了怎样的变化[6]或有限的病例系列报告[7-10]。面对新的疾病谱，疾病间的相互影响知之甚少。我们关注的科学问题是：COVID-19 感染是否会对脑卒中预后是否有影响？两者之间何种相互作用机制目前尚不明确。有部分学者认为 COVID-19 合并脑卒中的病因可能是血液的高凝状态[11]、继发于颅内细胞因子风暴的血管炎[12]和病毒本身的感染[13]等。基于此本研究旨在对这一全球关注问题进行 Meta 分析，通过分析 COVID-19 感染与脑卒中关系，进一步评估 COVID-19 感染对脑卒中病死率的影响，并对其可能机制进行探讨，从而为 COVID-19 患者的科学防治提供可靠的临床理论依据。

1 材料与方法

本 Meta 分析涉及的方法学均依据首选报告项目 (PRISMA) 声明完成[14]。

1.1 文献纳入与排除标准

1.1.1 研究类型：评价 COVID-19 对脑卒中死亡率的队列研究或病例对照研究；

1.1.2 研究对象：病例均根据世界卫生组织利用鼻咽拭子样品的逆转录聚合酶链反应建立的标准行 COVID-19 病毒检测；根据 2018 版中国急性缺血性脑卒中诊治指南被诊断为脑卒中；患者需完成入院时的 NIHSS 评估及住院期间的实验室检查及转归记录。

1.1.3 干预措施：病例组为 COVID-19 感染脑卒中患者；对照组为非 COVID-19 感染脑卒中患者；

1.1.4 文献中可以获得或推算出脑卒中的病死率；

1.1.5 排除标准：①数据不完整或统计分析不充分的研究被删除；②评论、评论和信件；③缺乏 COVID-19 和脑卒中诊断标准的信息；④重复发表文章或基于相同人口数据的多次调查，将最新的研究或信息全面的文章纳入；⑤病例报告和病例系列、基础研究或实验室研究等非临床研究类型文献。

1.2 检索策略 计算机检索 Pubmed，embase，web of science， cochrane，知网（China National Knowledge Infrastructure, CNKI）及万方等权威数据库，收集关于 COVID-19 患者脑卒中临床研究文献，检索时间为 2019 年 12 月至 2022 年 1 月。检索词采用主题词与自由词相结合方式，中文检索词为“COVID-19；脑卒中；新型冠状病毒；脑血管病；死亡率；”，英文检索词为“Coronavirus Disease 2019 Virus,Stroke, novel coronavirus; Cerebrovascular disease; Mortality”，同时手动检索纳入文章的相关参考文献，以尽可能全面纳入相关研究。

1.3 文献筛选、数据提取及文献质量评价

1.3.1 文献筛选 两名评价员通过筛选标题、摘要和全文来评估所有确定的文章，并以协商一致的方式解决任何分歧。全文评估是在摘要没有提供足够的信息来评估方法的情况下进行的。如果信息不完整或存在任何不明确之处，我们会联系相关文章的作者。见 Fig1

1.3.2 数据提取及文献质量评价 提取内容包括：第一作者、发表年份、研究国家、研究类型、样本量、住院病死率、美国国立美国国立卫生院神经功能缺损评分(National Institutes of Health Neurological Impairment Score, NIHSS)、年龄、实验室指标。同时利用 the Newcastle-Ottawa Scale (NOS)对纳入文献进行评估。

1.4 统计学分析 使用 RevMan 5.3 软件进行文献的异质性分析，异质性分析采用 I^2 检验，若 I^2<=50%，说明文献间的异质性较小，则采用固定效应模型对该研究结果进行 Meta 分析; I^2>50%则可以使用随机效应模型。如果异质性较高，则可以通过采用敏感性分析技术寻找异质性原因。计数资料总有效率用相对危险度（Relative Risk, RR）表示，计量资料用平均差(mean difference, MD)表示并计算 95%置信区间(confidence interval, CI)。当 P<0.05 时，差异具有统计学意义。绘制漏斗图分析报告发表偏倚可信度,并分析检验结果的敏感分析。

2. 结果

2.1 文献检索结果

本研究共检索出 2805 条文献，利用 endnote 筛选，最终纳入 20 篇文献[15-34]，均为英文文献。文献筛选流程及结果见图 1，所纳入文献的基本特征见表 1。

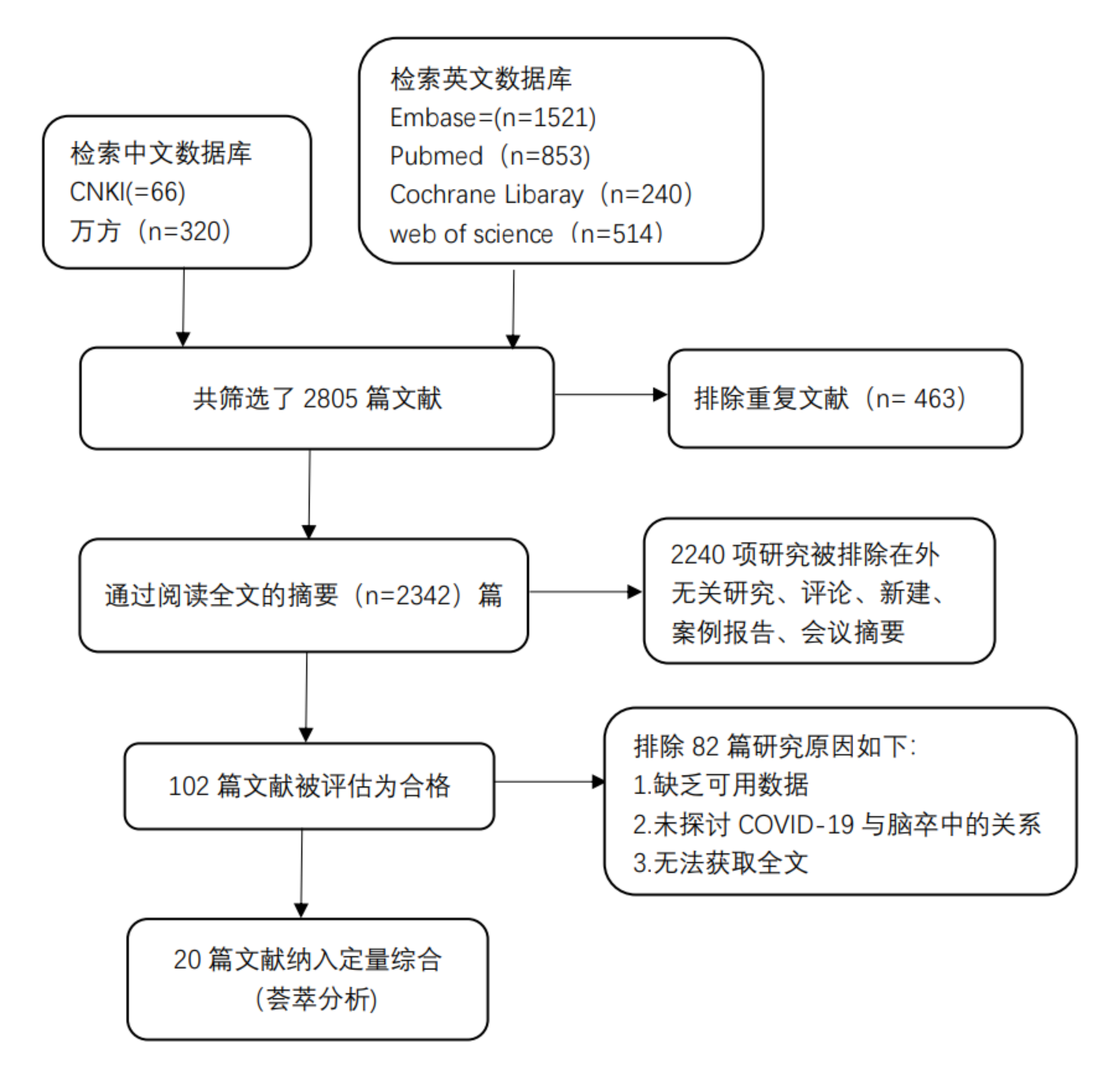


图 1 文献筛选流程图

Figure 1 Flow chart of literature screening

作者	发表年份	平均年龄		样本量		住院死亡人数		研究类型
		病例组	对照组	病例组	对照组	病例组	对照组	
Rohit Bhatia	2021	58.25±15.19	60.59±14.71	52	355	22	27	病例对照研究
hen Lin	2020	58.2±18.3	65.9±13.9	9	51	4	4	病例对照研究
Shadi Yagh	2020	-	-	32	46	14	4	队列研究
Fernando Sierra Hidalgo	2021	-	-	1673	873	-	-	队列研究
Pablo Naval-Baudin	2020	70.2±8.4	70.1±15.3	19	81	5	5	病例对照
M Mehrpour1	2020	75.60±9.54	60.86±18.45	10	21	3	2	病例对照研究

Jeffrey	2020	-	-	86	499	25	45	队列研究
Alberto Benussi	2020	-	-	43	68	15	4	队列研究
ThomasLijuan Zhang, Mathew	2021	55.66±13.20	57.21±11.97	60	104	13	0	病例对照对照
Joan Martí-Fàbregas	2021	71.6±12.3	72.4±13.5	91	610	38	98	队列研究
Kimon Bekelis	2020	-	-	2513	22295	-	-	队列研究
Adnan I. Qureshi	2021	68.8±15.1	71±14.9	8163	199	-	-	队列研究
Alexander E. 2020	2020	-	-	1916	1486	-	-	队列研究
Mandip S. Dhamoo	2021	65.9±14.3	66.7±15.5	105	172	35	22	队列研究
Mehmet Akif Topcuoglu	2021	-	-	37	355	18	22	病例对照研究
Richard J Perry	2020	-	-	23	177	-	-	病例对照研究
Seby John	2020	48.1±10.8	58.7 ±14.5	19	220	1	4	病例对照研究
Minghuan Wang	2021	-	-	124	226	34	5	队列研究
Ludovico Ciolli1	2021	-	-	26	111	7	10	病例对照研究
Eric Jorge	2021	-	-	748141388879		-	-	队列研究

表 1 纳入研究的基本特征

Table 1 Basic characteristic of the included literatures

2.2 质量评估结果

纳入的 20 项研究，符合“一般或良好”质量标准，被选中进行进一步分析 8 项研究符合“良好”质量标准，12 项符合“一般”质量标准。（见表 2）

	Selection	Comparison	Exposure	Score
Shadi Yagh 2020	4	1	1	6
Fernando Sierra-Hidalgo 2021	4	1	1	6
Jeffrey 2020	4	1	0	5
Alberto Benussi 2020	4	2	2	8
Joan Martí-Fàbregas 2021	4	0	3	7
Kimon Bekelis 2020	4	0	2	6
Adnan I. Qureshi 2021	4	1	1	6
Alexander E. 2020	4	0	2	6
Mandip S. Dhamoo 2021	3	2	3	8

Minghuan Wang 2021	4	0	2	6
Eric Jorge 2021	4	2	3	9

表 2 纳入队列研究的 NOS 评分情况

Table 2 NEWCASTLE-OTTAWA OUALITY ASSESSMENT SCALE CASE CONTROL STUDIES

	Selection	Comparison	Exposure	Score
Rohit Bhatia2021	4	1	1	6
Chen Lin 2020	4	1	3	8
Pablo Naval-Baudin 2020	4	1	2	7
Alberto Benussi 2020	4	2	2	8
Mandip S. Dhamoo 2021	3	2	3	8
Mehmet Akif Topcuoglu 2021	3	2	2	7
Richard J Perry 2020	3	2	2	7
Seby John 2020	4	2	3	9
Ludovico Ciolli1 2021	4	2	2	8

表 3 纳入病例对照研究的 NOS 评分情况

Table 3　NOS scores were included in case-control studies

2.3 Meta 分析结果

2.3.1

COVID-19 感染对脑卒中病死率的影响 其中 16 篇文献研究对 COVID-19 感染合并脑卒中患者的住院期间（<15 天）病死率进行报告，总计 4791 名患者，Meta 分析结果示：与非感染 COVID-19 患者相比，感染 COVID-19 的脑卒中患者有更高的死亡风险 (RR=4.16, 95% CI: 2.82-6.13)，结果见图 2，异质性结果为 I^2=84%，在随机效应模型分析下两组病死率差异具有统计学意义(P<0.001)；在我们纳入的各项研究中逐个剔除异质，敏感性分析结果没有显著差异证明该结果较为稳定。

2.3.2 COVID-19 感染对脑卒中患者 PT 的影响 其中 4 篇文献研究对 COVID-19 感染合并脑卒中患者入院时的 PT 进行报告，总计 889 名患者，Meta 结果为 MD=0.93, 95% CI: 0.26-1.60, I^2=50%，在随机效应模型分析下两组 PT 有差异 P=0.007(见图 3)；通过对纳入的各项研究中逐个剔除异质，异质敏感性分析结果没有显著差异证明该结果较为稳定。

2.3.3 COVID-19 感染对脑卒中患者 APTT 的影响 其中 4 篇文献研究对 COVID-19 合并脑卒中患者入院时的 APTT 进行报告，总计 968 名患者，Meta 分析结果提示 MD=2.51(95% CI: -2.69-7.71），结果见图 4，在随机效应模型分析下异质性为 I^2=83%，但该差异没有统计学意义(P=0.34)。

2.3.4 COVID-19 感染对脑卒中患者 D-二聚体的影响 其中 7 篇文献研究对 COVID-19 患者合并脑卒中入院时的 D-二聚体进行报告，总计 1100 名患者，Meta 分析结果示(MD=1.34, 95% CI: 4.54-8.79, I^2=59%)，结果见图 5，在随机效应模型分析下两组间 D-二聚体的差异有统计学意义 P<0.01；敏感性数据分析显示：通过对纳入的各项研究中逐个剔除异质，异质敏感性分析结果没有显著差异证明该结果较为稳定。

2.3.5 COVID-19 感染合并脑卒中患者 NIHSS 评估 其中 5 篇文献研究对 COVID-19 感染合并脑卒中患者入院时的 NIHSS 进行报告，总计 1141 名患者，Meta 结果为 MD=6.66, 95% CI: 4.54-8.79, I^2=59%，在随机效应模型分析下两组 PT 有差异 P<0.01(见图 6）表明 COVID-19 感染合并脑卒中患者的 NIHSS 高于对照组，对纳入的各项研究中逐个剔除异质，异质敏感性分析结果没有显著差异，证明该结果较为稳定。

2.3.6 COVID-19 感染合并脑卒中患者年龄的评估 其中 9 篇文献研究对 COVID-19 感染合并脑卒中患者的年龄进行报告，总计 2290 名患者，Meta 分析结果示：与非感染 COVID-19 患者相比，感染 COVID-19 的脑卒中患者年龄偏小（MD=-1.70, 95% CI: -3.11--0.28)，结果见图 7，异质性结果为 I^2=67%，在固定效应模型分析下两组年龄有差异 P=0.02；通过对纳入的各项研究中逐个剔除异质，异质敏感性分析结果没有显著差异证明该结果较为稳定。

Study or Subgroup	新冠人群合并卒中组 Events	新冠人群合并卒中组 Total	非新冠人群合并卒中组 Events	非新冠人群合并卒中组 Total	Weight	Risk Ratio M-H, Random, 95% CI
Adnan I. Qureshi 2021	20	103	43	199	8.0%	0.90 [0.56, 1.44]
Chen Lin 2020	4	9	4	51	4.9%	5.67 [1.72, 18.65]
Eric Jorge 2021	43	147	42	294	8.4%	2.05 [1.41, 2.98]
Jeffrey 2020	25	41	45	499	8.4%	6.76 [4.67, 9.80]
Joan Martí-Fàbregas 2021	38	91	98	610	8.7%	2.60 [1.92, 3.52]
Kimon Bekelis 2020	7	22	25	544	6.9%	6.92 [3.36, 14.25]
Ludovico Ciolli1 2021	7	26	10	111	6.3%	2.99 [1.26, 7.11]
M Mehrpour1 2020	3	10	2	21	3.5%	3.15 [0.62, 15.97]
Mandip S. Dhamoo 2021	35	105	22	172	8.0%	2.61 [1.62, 4.19]
Mehmet Akif Topcuoglu 2021	18	37	22	355	7.8%	7.85 [4.65, 13.24]
Minghuan Wang 2021	34	124	5	226	6.1%	12.39 [4.97, 30.88]
Pablo Naval-Baudin 2020	5	19	5	81	5.1%	4.26 [1.37, 13.26]
Rohit Bhatia 2021	22	52	27	355	8.0%	5.56 [3.44, 9.01]
Seby John 2020	1	19	4	220	2.4%	2.89 [0.34, 24.62]
Shadi Yagh 2020	14	22	4	43	5.7%	6.84 [2.55, 18.32]
Thomas Lijuan Zhang, Mathew 2021	13	62	0	111	1.6%	48.00 [2.90, 793.89]
Total (95% CI)		**889**		**3892**	**100.0%**	**4.16 [2.82, 6.13]**
Total events	289		358			

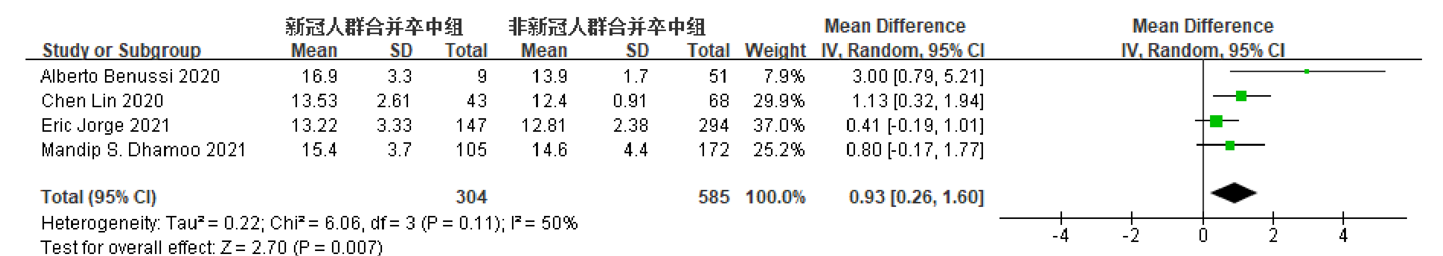
Heterogeneity: Tau² = 0.43; Chi² = 87.06, df = 15 (P < 0.00001); I² = 83%

Test for overall effect: Z = 7.19 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI (axis: 0.005, 0.1, 1, 10, 200)

Fig2 Case fatality rate of stroke in COVID-19 patients

RR Relative risk: 95%CI 95% confidence interval



Study or Subgroup	新冠人群合并卒中组 Mean	SD	Total	非新冠人群合并卒中组 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alberto Benussi 2020	16.9	3.3	9	13.9	1.7	51	7.9%	3.00 [0.79, 5.21]
Chen Lin 2020	13.53	2.61	43	12.4	0.91	68	29.9%	1.13 [0.32, 1.94]
Eric Jorge 2021	13.22	3.33	147	12.81	2.38	294	37.0%	0.41 [-0.19, 1.01]
Mandip S. Dhamoo 2021	15.4	3.7	105	14.6	4.4	172	25.2%	0.80 [-0.17, 1.77]
Total (95% CI)			**304**			**585**	**100.0%**	**0.93 [0.26, 1.60]**

Heterogeneity: Tau² = 0.22; Chi² = 6.06, df = 3 (P = 0.11); I² = 50%
Test for overall effect: Z = 2.70 (P = 0.007)

Fig3 The contrast of PT of stroke in COVID-19 patients

Mean Difference: 95%CI 95% confidence interval

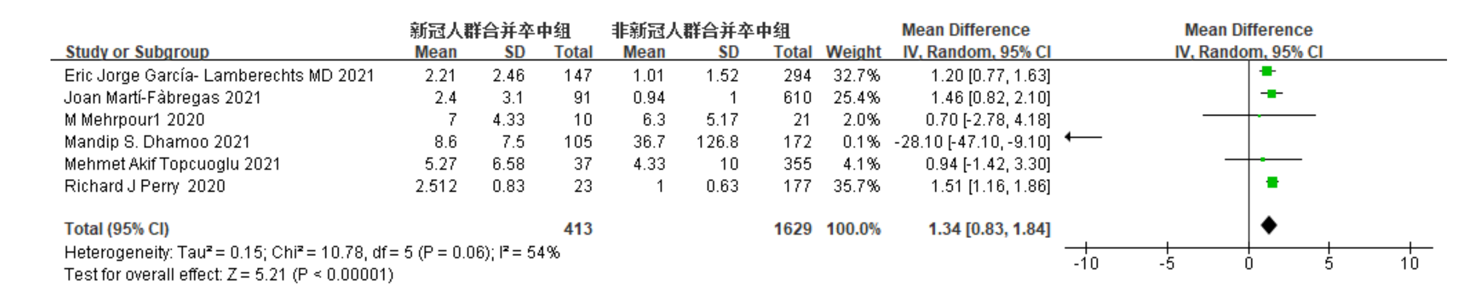
Study or Subgroup	新冠人群合并卒中组 Mean	SD	Total	非新冠人群合并卒中组 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Chen Lin 2020	40.9	15.4	9	29	5.2	51	3.1%	11.90 [1.74, 22.06]
Mandip S. Dhamoo 2021	38.9	24.8	105	31.1	13.4	172	11.9%	7.80 [2.65, 12.95]
Mehmet Akif Topcuoglu 2021	25.49	5.2	37	26.29	16.2	355	55.9%	-0.80 [-3.18, 1.58]
Seby John 2020	28.9	2.9	19	32.1	22.9	220	29.1%	-3.20 [-6.50, 0.10]
Total (95% CI)			**170**			**798**	**100.0%**	**-0.09 [-1.86, 1.69]**

Heterogeneity: Chi² = 18.13, df = 3 (P = 0.0004); I² = 83%
Test for overall effect: Z = 0.09 (P = 0.93)

Mean Difference IV, Fixed, 95% CI: -20 -10 0 10 20

Fig4 The contrast of APPT of stroke in COVID-19 patients

Mean Difference: 95%CI 95% confidence interval

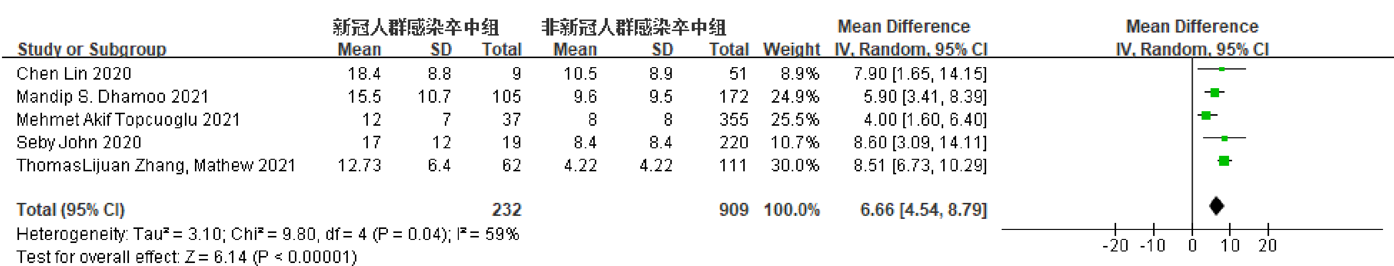


Study or Subgroup	新冠人群合并卒中组 Mean	SD	Total	非新冠人群合并卒中组 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eric Jorge García- Lamberechts MD 2021	2.21	2.46	147	1.01	1.52	294	32.7%	1.20 [0.77, 1.63]
Joan Martí-Fàbregas 2021	2.4	3.1	91	0.94	1	610	25.4%	1.46 [0.82, 2.10]
M Mehrpour1 2020	7	4.33	10	6.3	5.17	21	2.0%	0.70 [-2.78, 4.18]
Mandip S. Dhamoo 2021	8.6	7.5	105	36.7	126.8	172	0.1%	-28.10 [-47.10, -9.10]
Mehmet Akif Topcuoglu 2021	5.27	6.58	37	4.33	10	355	4.1%	0.94 [-1.42, 3.30]
Richard J Perry 2020	2.512	0.83	23	1	0.63	177	35.7%	1.51 [1.16, 1.86]
Total (95% CI)			**413**			**1629**	**100.0%**	**1.34 [0.83, 1.84]**

Heterogeneity: Tau² = 0.15; Chi² = 10.78, df = 5 (P = 0.06); I² = 54%
Test for overall effect: Z = 5.21 (P < 0.00001)

Fig5 The contrast of D-D of stroke in COVID-19 patients

Mean Difference: 95%CI 95% confidence interval



Study or Subgroup	新冠人群感染卒中组 Mean	SD	Total	非新冠人群感染卒中组 Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen Lin 2020	18.4	8.8	9	10.5	8.9	51	8.9%	7.90 [1.65, 14.15]
Mandip S. Dhamoo 2021	15.5	10.7	105	9.6	9.5	172	24.9%	5.90 [3.41, 8.39]
Mehmet Akif Topcuoglu 2021	12	7	37	8	8	355	25.5%	4.00 [1.60, 6.40]
Seby John 2020	17	12	19	8.4	8.4	220	10.7%	8.60 [3.09, 14.11]
ThomasLijuan Zhang, Mathew 2021	12.73	6.4	62	4.22	4.22	111	30.0%	8.51 [6.73, 10.29]
Total (95% CI)			**232**			**909**	**100.0%**	**6.66 [4.54, 8.79]**

Heterogeneity: Tau² = 3.10; Chi² = 9.80, df = 4 (P = 0.04); I² = 59%
Test for overall effect: Z = 6.14 (P < 0.00001)

Fig6 The contrast of NIHSS of stroke in COVID-19 patients

Study or Subgroup	新冠人群感染卒中组 Mean	SD	Total	非新冠人群感染卒中组 Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Adnan I. Qureshi 2021	68.8	15.1	103	71	14.9	199	15.7%	-2.20 [-5.78, 1.38]
Chen Lin 2020	58.2	18.3	9	65.9	13.9	51	1.3%	-7.70 [-20.25, 4.85]
Joan Martí-Fàbregas 2021	71.6	12.3	91	72.4	13.5	610	26.7%	-0.80 [-3.54, 1.94]
M Mehrpour1 2020	75.6	9.54	10	60.86	18.45	21	2.1%	14.74 [4.88, 24.60]
Mandip S. Dhamoo 2021	65.9	14.3	105	66.7	15.5	172	15.7%	-0.80 [-4.38, 2.78]
Pablo Naval-Baudin 2020	70.2	8.4	19	70.1	15.3	81	7.9%	0.10 [-4.94, 5.14]
Rohit Bhatia 2021	58.25	15.19	52	60.59	14.71	355	10.4%	-2.34 [-6.74, 2.06]
Seby John 2020	48.1	10.8	19	58.7	14.5	220	7.4%	-10.60 [-15.82, -5.38]
ThomasLijuan Zhang, Mathew 2021	55.66	13.2	62	57.21	11.97	111	12.8%	-1.55 [-5.52, 2.42]
Total (95% CI)			**470**			**1820**	**100.0%**	**-1.70 [-3.11, -0.28]**

Heterogeneity: Chi² = 24.03, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 2.34 (P = 0.02)

Mean Difference IV, Fixed, 95% CI: -10 -5 0 5 10

Fig7 The contrast of age of stroke in COVID-19 patients

2.4 偏倚分析

本研究主要以对脑卒中的病死率改变绘制漏斗图来评价发表偏倚，由漏斗图可以看出（见图 8），纳入的研究对象在轴线两侧基本对称分布，不存在发表偏倚，较为对称，实验结果可信度较高。

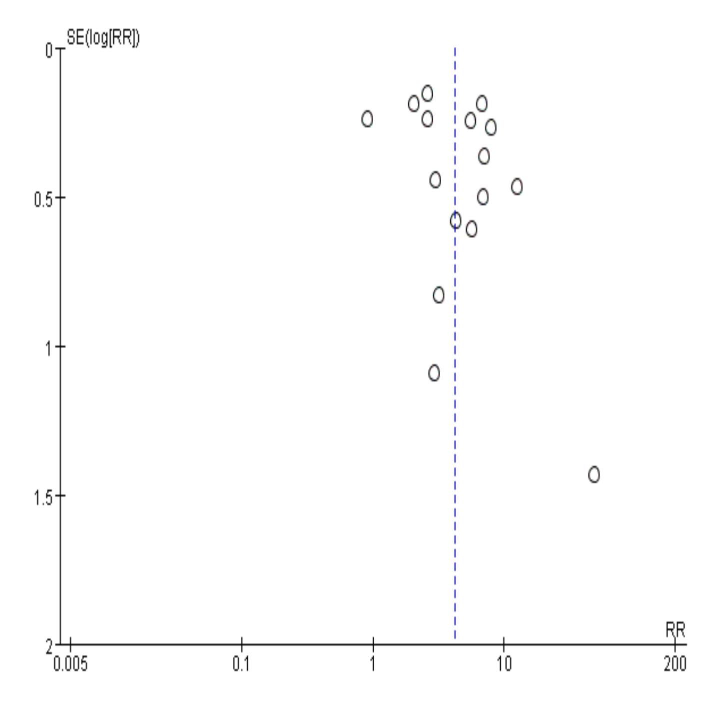


Fig 8 Funnel plot comparing the level of mortality among patients

3. 讨论

COVID-19 是由 2019 年 12 月在中国武汉首次报道的严重 SARS-CoV-2 引起的疾病，并已在全世界蔓延。至 2021 年 12 月为止，COVID-19 影响了 224 个国家和地区的 27.8 亿人，造成 530 万人死亡[35]。随着 Omicron[36]等变体的出现，COVID-19 病例呈指数增长，导致数千人死亡。且此病可累及多个系统受损，在脑卒中的发病中也扮演者着重要角色[37]。面对新的疾病谱，疾病间的相互影响知之甚少。许多病例报告研究表明，COVID-19 感染可导致血栓性疾病，而脑卒中与血栓事件密切相关，COVID-19 感染对脑卒中的预后是否有影响？两者之间何种相互作用机制目前尚不明确。

在 COVID-19 大流行期间，许多国家报告脑卒中患者入院人数急剧减少，这表明症状轻微的脑卒中患者未入院或者由于担心 COVID-19 感染，他们自发地宁愿待在家里，在人口封锁期间不联系医疗援助，这与 NOT 等人报道的各个地区脑卒中住院率减少相符[38]。与 2019 年同期相比，2020 年研究期间脑卒中入院率下降 45%以下。所有患者均为 COVID-19 阳性，这种脑卒中患者入院率降低可能与疫情期间更侧重于 COVID-19 患者的转移相关，从而无法得出脑卒中发病的增加或减少与 COVID-19 之间的明确关系。本 Meta 分析发现在脑卒中患者中，COVID-19 感染患者比非 COVID-19 感染患者的病死率明显升高，差异有统计学意义(RR=4.16, 95% CI: 2.82-6.13, I^2=83%, P<0.001)。这和一项荟萃分析相一致[39]，与非 COVID-19 感染患者相比，COVID-19 感染导致脑卒中的死亡风险增加 3 倍。同时 YANG 等人的研究表明既往的脑血管疾病与 COVID-19 患者预后不良风险增加相关[40]，可能是由于严重的潜在

感染以及随之而来的全身和代谢功能障碍所致。

本分析发现在脑卒中患者中，感染 COVID-19 与非感染 COVID-19 患者相比凝血指标异常率更高，且差异有统计学意义（MD=0.93, 95% CI: 0.26-1.60; MD=1.34, 95% CI: 0.83-1.84, I^2=54%)。与我们的分析结果相一致的是 Garica 报道，合并 COVID-19 感染的脑卒中患者比普通患者的 D-二聚体水平更高，淋巴细胞计数更高低，这表明 COVID-19 感染会引起免疫水平下降[41]。同时来自中国的一项报告描述了合并脑卒中的 COVID-19 感染患者，其抗磷脂抗体和 D-二聚体异常率更高[42]。其中 D-二聚体是血栓形成后，纤维蛋白溶解系统将纤维蛋白网分解，由纤维蛋白的两个 D 段组成的一个聚合体[43]，它代表纤维蛋白溶解系统的激活，也有研究表明[44]，D-二聚体和纤维蛋白原水平的增加与疾病的严重程度和病死率增加有关。此外发现 APTT 在 COVID-19 感染患者和普通患者中无明显差异学意义。PT 是反应外源性凝血途径的试验，正常范围是 11-13s，改变正常对照 3s 以上有临床意义，PT 缩短，说明机体存在着高凝状态，容易发生血栓性的疾病，如冠心病、心肌梗死、深静脉血栓。PT 延长，而 APTT 是反应内源性凝血途径的功能，根据纳入的研究 170 个 COVID-19 患者和 798 个非 COVID-19 患者引发的脑卒中，结果显示两者间并无明显统计学差异。

部分文献报道 COVID-19 感染合并脑卒中患者的 NIHSS 及年龄等,其中调整相关变量分析中发现 NIHSS、年龄与住院病死率相关。在我们的脑卒中病例系列中，COVID-19 感染病例的平均年龄更低，((MD=-1.70, 95% CI: -3.11--0.28）,P=0.02)，NIHSS 评分较高（MD=6.66, 95% CI: 4.54-8.79, P<0.01)。这项研究的一个主要发现是，脑卒中的严重程度也受 COVID-19 感染显著影响,与无 COVID-19 感染的脑卒中患者相比，有 COVID-19 的患者卒中严重程度明显更高,且住院病死率较高。

然而 COVID-19 患者发生脑卒中的机制仍有待确定，目前有几个合理的假设：血管壁侵入、凝血障碍、继发于心肌损伤的脑栓塞或现有动脉粥样硬化斑块的不稳定。该病毒能够侵入血管壁，因为内皮细胞表达 ACE2 受体[45]，病毒利用该受体进入细胞，通过破坏血管壁或诱导抗磷脂抗体促进血栓形成[46]，也可通过激活免疫系统导致血栓形成[47]，从而影响凝血、血小板活化和内皮功能导致机体处于高凝状态。另一种潜在机制是干扰凝血[48]，COVID-19 感染一方面引起内皮细胞损伤从而激活组织因子-□a 因子途径启动凝血，并在病变区域募集血小板和白细胞增加局部炎症进一步促进凝血系统的激活。一些病毒还可以同时病毒另外在某些 COVID-19 感染患者中引起的一般炎症状态或"细胞因子风暴" 影响着机体凝血功能[49]。COVID-19 感染合并脑卒中后死亡率增加可能是全身性高凝的表现，它打破了体内凝血和抗凝系统的平衡，增加了脑卒中的风险[50]。有一些报道发现对与 COVID-19 患者预防性抗凝治疗可以明显降低全身血栓事件的发病率[51]，也有一些报道称，抗凝治疗会减少脑卒中的死亡风险[52]。

本文系统分析了目前已有的小样本回顾性研究，与非 COVID-19 感染患者相比，COVID-19 感染患者的脑卒中与更高的住院病死率相关。该预后与实验室指标如凝血指标（D-二聚体、PT）明显相关，也与脑卒中的严重程度及年龄相关，为 COVID-19 合并脑卒中患者早期识别及治疗开辟新的途径，并提供了循证依据。本次 Meta 分析存在一定的局限性，如纳入的患者样本量偏小；纳入文献均未提及盲法的使用及分配隐藏，易发生选择性偏倚；纳入文献关于正念干预的方法不够详细系统； COVID-19 在脑卒中患者中的发病率仍需要高质量的随机对照研究证实。

本文无利益冲突。

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